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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,197	04/04/2005	William J Cairns	P51332	4501

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EXAMINER	
CRUZ, KATHRIEN ANN	

ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
12/09/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/509,197	CAIRNS ET AL.	
	Examiner	Art Unit	
	KATHRIEN CRUZ	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-34* is/are pending in the application.

4a) Of the above claim(s) *29,30 and 32-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/22/2004, 05/04/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 28-34 are pending.

Claims 29-30 and 32-34 are withdrawn.

Claims 28 and 31 are examined herewith.

Applicant's election without traverse of Group III in the reply filed on September 11, 2009 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of amyotrophic lateral sclerosis with the administration of Example 3: ((R)-2-(3-{3-[[2-Chloro-3- (trifluoromethyl)benzyl](2,2-diphenylethyl)amino]-1-methyl-propoxy}-phenyl)acetic acid methyl ester) and Example 1: 2-(3-{3-[[2-Chloro-3-(trifluoromethyl)benzyl](2-2-diphenylethyl)amino] propoxy}-phenyl)acetic acid, does not reasonably provide enablement for all LXR agonist in the treatment of amyotrophic lateral sclerosis.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art

and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: Claims 28 and 30 are drawn to a method of treating amyotrophic lateral sclerosis (ALS)) by administering a LXR agonist.

Breadth of the claims: The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass prevention of neurological disorders in mammals which have potentially many different pathogenesis of amyotrophic lateral sclerosis (ALS) are not known, although a number of hypotheses have been advanced. The claims recite that not only amyotrophic lateral sclerosis (ALS) can be treated with Example 3: ((R)-2-(3-{3-[[2-Chloro-3-(trifluoromethyl)benzyl](2,2-diphenylethyl)amino]-1-methyl-propoxy}-phenyl)acetic acid methyl ester) and Example 1: 2-(3-{3-[[2-Chloro-3-(trifluoromethyl)benzyl](2-2-diphenylethyl)amino] propoxy}- phenyl)acetic acid but that it can also be **treated with any LXR agonist**.

Guidance of the Specification/Working Examples: Applicant has provided no guidance showing the actual data that any LXR agonist may treat amyotrophic lateral sclerosis (ALS). All the guidance are directed to the treatment of ALS with Example 1: 2-(3-{3-[[2-Chloro-3-(trifluoromethyl)benzyl](2-2-diphenylethyl)amino] propoxy}-phenyl)acetic acid. All of the working examples disclosed by the applicants utilizing stem cells and pancreatic cells with only the composition of Example 1. There are no working examples utilizing any other composition as claimed in the instant application.

Predictability/Unpredictability in the Art: There *is a general lack of predictability in the pharmaceutical art. In re Fisher, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970). It would be unpredictable for the skilled artisan to use the claimed formulation to treat all forms of amyotrophic lateral sclerosis (ALS) with any LXR agonist because of the reasons stated above.*

The Quantitation of Experimentation Required: In order to practice Applicants invention, it would be necessary for one to conduct an exhaustive amount of experiments. Applicant would need to provide reasonable data showing that any LXR agonist would treat amyotrophic lateral sclerosis (ALS). Therefore, in order to practice the claimed invention, the amount of experimentation required would be considered undue and burdensome.

According, the method of treating ALS with any LXR agonist is not enabled by the instant specification.

Claims 31 is rejected under 35 U.S.C.112, first paragraph, because the specification , while being enabling for making and using salts of the claimed compounds, does not reasonable provide enablement for making and using solvates of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill

of those in that art, g) the predictability or unpredictability of tat art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni,* 195 USPQ 150, *ex parte formal,* 230 USPQ 546. a) Finding a solvates or hydrates is an empirical exercise. Predicting if a certain ester of claimed alcohol, for example, is in fact a solvates that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo* , this is still an experimental science. For a compound to be a solvates, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the solvates is found in the specification on page 21. c) There is no working example of a solvates of a compound the formula III. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrugs art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to fine a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicated the low

expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the solvates concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence is particularly relevant. f) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F2d 833, 839, 166 USPQ 18, 24 (CCPQ 1970). g) The breadth of the claims includes all of the hundreds of thousand of compounds of formula III of claim 31 as well as the presently unknown list of potential solvates embraced by claim 31.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

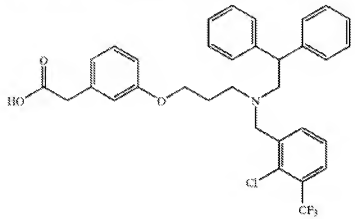
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 28 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Collins et al (US 2004/0072868) and Dietschy (Cholesterol metabolism in the brain, Current Opinion in Lipidology, 12(2): 105-112, 2001) both are of record and in further view of Yamashita (Concurrence of amyotrophic lateral sclerosis with limbic degeneration and Alzheimer's disease, Neuropathology 1997: 17, pages 334-339).

Collins et al discloses the following compound as shown below (see col. 18, ex. 16):

EXAMPLE 16

[0315] 2-(3-{3-[[2-Chloro-3-(trifluoromethyl)benzyl](2,2-diphenylethyl)amino]propoxy}-phenyl)acetic Acid



Collins teaches the treatment with the above mention composition for cardiovascular disease, increasing HDL cholesterol, inhibiting cholesterol absorption and treating LXR mediated diseases and conditions (paragraph 0004 and claims 28-30).

Collins does not expressly teach the treatment of amyotrophic lateral sclerosis (ALS).

Dietschy teaches that the several lines of evidence suggest a relationship between the circulating plasma cholesterol concentration and the onset of neurodegeneration (page 110, left column, first paragaraph). Dietschy teaches that the observations that changes in cholesterol balance across cells affects both the rate of processing of proteins such as APP and the level of apoE in the CNS may explain the findings that cholesterol feeding enhances the rate of neuritic plaque formation in the brain, whereas the administration of inhibitors of cholesterol synthesis apparently

markedly reduces the prevalence of Alzheimer's disease (page 109, right column, third paragraph).

Yamashita teaches that amyotrophic lateral sclerosis with limbic degeneration and Alzheimer's disease occurs simultaneously in some individuals (introduction, page 337, right column, second paragraph).

It would have been obvious to one of ordinary skills in the art to employ the teachings of Dietschy and Yamashita to that of Collins for the treatment of ALS. One would have been motivated to employ the treatment of ALS with LXR agonist because Collins teaches that the LXR agonist is useful in the inhibition of cholesterol absorption and treating LXR mediated diseases and conditions. Dietschy teaches that the observations that changes in cholesterol balance across cells affects both the rate of processing of proteins such as APP and the level of apoE in the CNS may explain the findings that cholesterol feeding enhances the rate of neuritic plaque formation in the brain, whereas the administration of inhibitors of cholesterol synthesis apparently markedly reduces the prevalence of Alzheimer's disease. And Yamashita teaches that amyotrophic lateral sclerosis with limbic degeneration and Alzheimer's disease occurs simultaneously in some individuals. Therefore, it would have been obvious to treat both Alzheimer's disease as well as ALS with an LXR agonist because administration of inhibitors of cholesterol synthesis apparently markedly reduces the prevalence of Alzheimer's disease and both are CNS disorders as taught by Collins and Dietschy. Additionally, it is known in the art that upon administration of LXR agonist inhibits the cholesterol absorption as taught by Collins. Dietschy teaches that cholesterol balance

changes the rate of proteins such as APP and ApoE which controls the rate of neuritic plaque formation and the reduction of the plaque formation significantly reduces the prevalence of Alzheimer's disease, therefore it would have been obvious to administer an LXR agonist to inhibit the amount of cholesterol that is absorb to so that the formation of plaque is reduce. Furthermore, since Yamashita teaches that amyotrophic lateral sclerosis with limbic degeneration and Alzheimer's disease occurs simultaneously in some individuals, it would have been obvious to treat ALS and Alzheimer's disease with LXR agonist.

For these reasons, the claimed subject matter is deemed to fail to be patentably distinguishable over the state of the art as represented by the cited reference. The claims are therefore, properly rejected under 35 U.S.C. 103.In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Claims 28 and 31 are rejected.

No claims are allowed.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHRIEN CRUZ whose telephone number is (571)270-5238. The examiner can normally be reached on Mon - Thurs 7:00am - 5:00pm with every Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KATHRIEN CRUZ/
Examiner, Art Unit 1628

/San-ming Hui/
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